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JC18 Rec'd PCT/PTO 17 MAY 2005

**VERIFICATION OF TRANSLATION**

I undersigned, Ms. Montse LOPEZ

Of C. Consell de Cent, 322; 08007 Barcelona; Spain

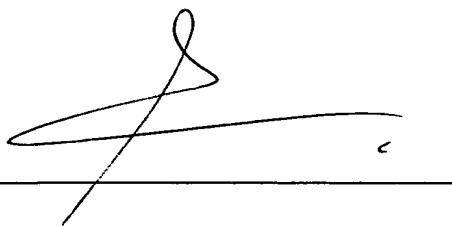
declare as follows:

1. That I am well acquainted with both the English and Spanish languages, and
2. That the attached document is a true and correct translation into English made by me to the best of my knowledge and belief of:

The Spanish patent nº P-200202963 filed on December 5, 2002

Barcelona, May 9, 2005

Signature of Translator: \_\_\_\_\_

A handwritten signature in black ink, appearing to read "Montse Lopez", is written over a horizontal line. The signature is fluid and cursive.

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## **OFFICIAL CERTIFICATE**

I certify herewith that the attached documents are a faithful copy to the original PATENT application Nr. 200202963, which was filed in this Organization on December 5<sup>th</sup>, 2002.

Madrid, 25 November 2003

Director of Patent and  
Technological Information Department  
P.D.

(signature)

CARMEN LENCE REIJA

MINISTRY OF SCIENCE  
AND TECHNOLOGY

OFFICIAL APPLICATION REQUEST

		Application number <b>P200202963</b>						
(1) MODALITY <input checked="" type="checkbox"/> PATENT		□ UTILITY MODEL						
(2) TYPE OF APPLICATION <input type="checkbox"/> PATENT ADDITION <input type="checkbox"/> DIVISIONAL APPLICATION <input type="checkbox"/> CHANGE OF MODALITY <input type="checkbox"/> EUROPEAN PATENT APPLICATION TRANSFORMATION <input type="checkbox"/> PCT: ENTRY INTO NATIONAL PHASE		(3) MAIN FILE OR FILE OF ORIGIN: MODALITY: APPLICATION NUMBER: FILING DATE:		05 DEC. 2002 Date and time of filing in the O.E.P.M.				
				Date and time of filing in a place other than O.E.P.M				
		(4) PLACE OF FILING BARCELONA		CODE 08				
(5) APPLICANT/S: SURNAMES OR COMPANY NAME PROYECTO EMPRESARIAL BRUDY, S.L.		NAME		NACIONALITY SPANISH	COUNTRY CODE ES	PERSONAL IDENTITY NR./ COMPANY IDENTIFICATION NR B61886214	CNAE	PYME
(6) FIRST APPLICANT'S DETAILS		TELEPHONE NR.: FAX NR.: E-MAIL: POSTAL CODE: 08006 COUNTRY CODE: ES NATION CODE: ES						
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(7) INVENTOR/S: FAMILY NAMES DOMINGO PEDRAL DOMINGO PEDRÀN		NAME Juan Carlos Pere		CITIZENSHIP SPANISH SPANISH		COUNTRY COD. ES ES		
(8) <input type="checkbox"/> APPLICANT AND INVENTOR ARE THE SAME PERSON <input checked="" type="checkbox"/> THE APPLICANT IS NOT THE INVENTOR OR AT LEAST IS NOT THE ONLY INVENTOR		(9) OBENTION OF RIGHTS OF INVENTION: <input checked="" type="checkbox"/> WORK INVENTION <input type="checkbox"/> CONTRACT <input type="checkbox"/> ASSIGNMENT						
(10) TITLE OF INVENTION USE OF DOCOSAHEXANOIC ACID AS ACTIVE SUBSTANCE FOR THE TREATMENT OF LIPODYSTROPHY								
(11) DEPOSIT OF BIOLOGICAL MATTER:		<input type="checkbox"/> YES		<input type="checkbox"/> NO				
(12) OFFICIAL EXPOSURES: PLACE		DATE:						
(13) PRIORITY: COUNTRY OF ORIGIN		COUNTRY CODE		NUMBER		DATE		
(14) THE APPLICANT AVAILS HIMSELF/HERSELF OF THE POSTPONED PAYMENT OF TAXES ACCORDING TO ART. 162 PATENT LAW 11/86 <input type="checkbox"/>								
(15) REPRESENTATIVE: FULL NAME AND ADDRESS (IF PROPERTY AGENT, NAME AND CODE) (PLEASE, FILL IN ONLY IF PROFESSIONAL): Ponti Sales, Adelaida, 388/3, Consell de Cent, 322, Barcelona, 08007, España								
(16) LIST OF ATTACHED DOCUMENTS:  <input checked="" type="checkbox"/> DESCRIPTION. NR. OF PAGES: 9 <input checked="" type="checkbox"/> NUMBER OF CLAIMS: 13 <input type="checkbox"/> DRAWINGS. NR. OF PAGES: <input type="checkbox"/> LIST OF SECUENCES. NR. OF PAGES: 0 <input checked="" type="checkbox"/> ABSTRACT <input type="checkbox"/> PRIORITY DOCUMENT <input type="checkbox"/> TRANSLATION OF PRIORITY DOCUMENT  <input checked="" type="checkbox"/> REPRESENTATION DOCUMENT <input checked="" type="checkbox"/> RECEIPT OF APPLICATION FEES' PAYMENT <input checked="" type="checkbox"/> COMPLEMENTARY INFORMATION SHEET <input type="checkbox"/> DRAWINGS SKETCHES <input type="checkbox"/> PROSPECTION QUESTIONNAIRE <input checked="" type="checkbox"/> OTHERS: DECLARATION OF INVENTOR							APPLICANT'S OR REPRESENTATIVE'S SIGNATURE  ADELAIDA PONTI SALES Member Nr. 320  (See communication)	
NOTIFICATION OF PAYMENT OF THE FEE FOR GRANT Please be informed that this application shall be withdrawn if the fee for grant is not duly paid; in order to do this payment there is a 3 months' time limit from the date of publication of the grant in the BOPI, and ten more days according to Art. 81 of R.D. 2245/1986							Government employee signature	

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APPLICATION NUMBER

P200202963

DATE OF FILING

## ABSTRACT AND DRAWING

ABSTRACT (Max. 150 words)

### USE OF DOCOSAHEXANOIC ACID AS ACTIVE SUBSTANCE FOR THE TREATMENT OF LIPODYSTROPHY

Use of an extract of animal, plant or microorganism-produced origin comprising docosahexaenoic acid as active substance for the manufacture of a medicament for the treatment of lipodystrophy in a mammal. Said treatment is effective and overcomes the disadvantages of current lipodystrophy treatments in HIV-infected patients.

GRAPHIC

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## PATENT APPLICATION

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31. NUMBER	PRIORITY DATA 32. DATE	33. COUNTRY	22. DATE OF FILING 05/12/2002
71. APPLICANT/S PROYECTO EMPRESARIAL BURDY, S.L. ADDRESS: C. Riera Sant Miquel, 3, 2n 4a. BARCELONA			62 PATENT OF ORIGIN DIVISORIA
72. INVENTOR/S JUAN CARLOS DOMINGO PEDRAL, PERE DOMINGO PEDRAL			
51. INT. CL.	GRAFIC (For abstract interpreting only)		
47. TITLE OF THE INVENTION  <b>USE OF DOCOSAHEXANOIC ACID AS ACTIVE SUBSTANCE FOR THE TREATMENT OF LIPODYSTROPHY</b>			
57. ABSTRACT  <b>USE OF DOCOSAHEXANOIC ACID AS ACTIVE SUBSTANCE FOR THE TREATMENT OF LIPODYSTROPHY</b>  Use of an extract of animal, plant or microorganism-produced origin comprising docosahexanoic acid as active substance for the manufacture of a medicament for the treatment of lipodystrophy in a mammal. Said treatment is effective and overcomes the disadvantages of current lipodystrophy treatments in HIV-infected patients.			

USE OF DOCOSAHEXANOIC ACID AS ACTIVE SUBSTANCE FOR THE  
TREATMENT OF LIPODYSTROPHY

5 FIELD OF THE INVENTION

This invention relates to the use of an extract of animal, plant or microorganism-produced origin comprising docosahexaenoic acid as active substance for the manufacture of a medicament for the treatment of lipodystrophy, particularly in patients infected by the HIV virus.

BACKGROUND OF THE INVENTION

15

Treatments have been available since the end of 1996 which are capable of controlling multiplication of the human immunodeficiency virus (HIV), which is the cause of acquired immune deficiency syndrome (AIDS). These 20 treatments have been generically so-called highly active anti-retroviral therapy (HAART). The current HAART characteristically consists in the combination of at least three drugs.

There are at present two families of 25 antiretrovirals that inhibit key enzymes for viral replication and which are the reverse transcriptase inhibitors (nucleoside analogues, nucleotide analogues and nucleoside non-analogues) and the viral protease inhibitors.

30 However, such treatments are not capable of leading to eradication of the virus (elimination thereof) and, to keep the infection controlled they, therefore, have to be administered indefinitely, probably throughout the patient's entire lifetime.

Such treatments, of undoubted efficacy in controlling viral replication, are nevertheless not innocuous for patients, and because the exposure time thereto is, necessarily, very lengthy, their toxic effects 5 tend to accumulate over time.

Since 1997 there began to be detected patients submitted to HAART who presented disorders not previously described in body-fat distribution, accompanied by plasma lipid level disorders.

10 Briefly, the patients show loss of fat in the face, buttocks, extremities and thorax, accompanied by accumulation of fat inside the abdomen, the back of the neck and in the breast area in women, together with increase plasmatic levels of cholesterol, triglycerides, 15 lowering of HDL cholesterol (protective cholesterol) and increase of LDL cholesterol (harmful cholesterol), insulin resistance (occasionally diabetes) and occasionally arterial hypertension.

This entire set of situations is known as 20 lipodystrophy syndrome.

Approaches to the treatment of lipodystrophy can be summed up in five broad groups:

(a) Strategies which modify the HAART components, so that this cannot be suppressed without running the risk 25 of losing control over viral replication.

(b) Drugs (e.g. methformine, rosiglytazone) which cause sensitisation to the action of insulin.

(c) Drugs which aim to control the lipidic aspects of the syndrome, such as fibrates and statines, which can 30 improve (though rarely normalise) plasmatic lipid disorders.

(d) Hormone treatments (e.g. growth hormones).

(e) Facial cosmetic surgery with implants to correct fat loss.

None of the treatments tested so far have shown any efficacy in reversing the disorders in body fat distribution, and the control of lipidic disorders using such measures has been incomplete.

5 It should be mentioned that the foregoing tested pharmacological treatments are not without toxic effects on the patient, which can, occasionally, be serious. They furthermore, mean an additional drug burden, and some of them interact in a potentially serious way with the 10 antiretroviral drugs which HIV-infected patients cannot stop taking.

There is still, therefore, no available treatment for lipodystrophy, in particular in HIV-infected patients, which is effective and does not give rise to the 15 disadvantages of the treatments currently known.

#### DESCRIPTION OF THE INVENTION

The inventors of the present invention have found 20 a treatment effective against lipodystrophy and which, furthermore, overcomes the disadvantages presented by the current treatments for said illness in HIV-infected patients.

This invention relates to the use of an extract of 25 animal, plant or microorganism-produced origin that comprises docosahexaenoic acid as active substance for the manufacture of a medicament for the treatment of lipodystrophy in a mammal.

Docosahexaenoic acid (DHA) is an omega-3 fatty 30 acid which contains 22 atoms of carbon, being six of them unsaturated (C22:6 n-3). Such acid is found, mainly, in fish (for example, tuna), microorganisms and plants.

In this invention, "extract of animal, plant or microorganism-produced origin that comprises 35 docosahexaenoic acid as active substance" is taken to mean

a composition which includes docosahexaenoic acid, which is obtained from fish, microorganisms and plants, by means of extraction, and optionally, chemical-modification procedures known to those skilled in the art.

5 In this invention, "microorganism" is taken to mean any microscopic organism, including but not limited to bacteria, protozoa, fungi, viruses and algae, and any of their variants produced by genetic engineering, which are characterized in that they produce DHA.

10 Docosahexaenoic acid can, thus, be one occurring naturally or one modified chemically. The chemical forms in which the DHA can be found therefore include, but are not restricted to, the free acid of DHA, DHA esters with natural or synthetic alcohols and lipidic forms such as 15 the glycerides, phospholipids, sphingolipids and gangliosides.

In particular, this invention relates to the use of an extract of animal, plant or microorganism-produced origin that comprises docosahexaenoic acid as active 20 substance for the manufacture of a medicament for the treatment of lipodystrophy in mammals, said extract having a DHA content that ranges between 5% and 100% (w/w), preferably between 50% and 100% (w/w).

Surprisingly, the inventors of the present 25 invention have found that the fact that the DHA is a physiological substance possessing multiple actions on the adipocytes (fat cells) and on plasma lipid levels permits the effective treatment of lipodystrophy.

Principal among these is its ability to promote 30 differentiation (multiplication) of the adipocytes, reduce blood triglyceride and cholesterol levels, increase HDL cholesterol level, reduce LDL cholesterol level, and reduce arterial blood pressure.

Additionally, the DHA possesses anti-inflammatory 35 properties (it inhibits the secretion of alpha tumour

necrosis factor) which, as will be shown below, is high in patients with lipodystrophy.

In a second aspect, a dosage of the medicament of the invention is administered equal to or higher than 100 5 mg/day, a dosage of 4 grams per day being preferable.

A medicament according to this invention can be administered orally or parenterally.

Depending on the chosen route of administration, pharmaceutically acceptable diluents, excipients and/or 10 carriers of the active substance can be included, such as liposomes, microemulsions, micelles, etc.

In a third aspect, the medicament of the invention is administered to a human, preferably an HIV-infected human.

15 It has been found, indeed, that administration of the medicament of the invention in cultured adipocytes is capable of inhibiting the toxic effects caused by the exposure of these cells to the antiretroviral drugs.

Therefore, and taking into account the beneficial 20 effects pointed out above, the medicament of this invention can perform a beneficial action on lipodystrophy syndrome, especially in HIV-infected patients treated under HAART regimens, having the following advantageous aspects in relation to current treatments:

25 1. adipocytary differentiation promoter activity;  
2. hypolipemiant activity;  
3. anti-inflammatory activity (reduction of the alpha tumour necrosis factor);  
4. antihypertensive activity;

30 5. absence of side effects at the dosages administered;

6. absence of interactions with the antiretroviral regimen components due to it being a medicament that is not metabolised by routes common to those of the

antiretroviral drugs (it should be remembered that the patient cannot dispense with HAART).

There follows, by way of non-restrictive illustration, an example of embodiment of this invention.

#### EXAMPLES

##### 10 Example 1

Four HIV-infected patients under HAART regimen and presenting lipodystrophy syndrome were administered 4 grams/day of a tuna oil with a DHA content of 70%. After 15 three months' administration of DHA to said patients, the following discoveries were made, even taking account of the short period of administration:

1. Partial reversal of body-fat distribution disorders, with
  - 1.1 improvement in facial fat loss;
  - 1.2 improvement in fat loss in buttocks and extremities;
  - 1.3 no increase in intra-abdominal fat.
- 25 2. Mean reduction of 56% in the plasma triglycerides number.
3. Mean reduction of 25% in the total plasma cholesterol number.
4. Mean increase of 9% in the plasma HDL cholesterol number.
- 30 5. Mean reduction of 18% in the plasma LDL cholesterol number.

These results, shown in the table on the following page, allow us to conclude that the administration of DHA

at dosages of 4 grams a day over the course of 3 months is capable of improving lipodystrophy and the lipidic disorders associated with it.

Table

	before the treatment				after 3 months of treatment					
	VLDL	COL.	TG	HDL	LDL	VLDL	COL.	TG	HDL	LDL
Patient 1	1.27	6.8	7.1	1.1	3.67	0.46	5.46	1	1.57	3.43
Patient 2	3.96	9.95	8.62	1.12	4.87	3.74	9.48	10.66	0.91	3.35
Patient 3	2.18	5.18	6.29	1.09	1.91	0.8	3.82	1.73	1.05	1.97
Patient 4	11.41	19.13	30.8	1.92	0.79	1.82	9.9	3.41	0.98	6.67

CLAIMS

5        1. Use of an extract of animal, plant or microorganism-produced origin that comprises docosahexaenoic acid as active substance for the manufacture of a medicament for the treatment of lipodystrophy in a mammal.

10        2. Use according to Claim 1, characterised in that the amount of docosahexaenoic acid in said extract is higher than or equal to 100 mg/day.

15        3. Use according to Claim 2, characterised in that said amount of docosahexaenoic acid in said extract is 4 grams/day.

        4. Use according to any of claims 1 to 3, in which the medicament promotes adipocytary differentiation.

        5. Use according to any of claims 1 to 3, in which the medicament has hypolipemiant activity.

20        6. Use according to any of claims 1 to 3, in which the medicament reduces the alpha tumour necrosis factor.

        7. Use according to any of claims 1 to 3, in which the medicament has antihypertensive activity.

25        8. Use according to Claim 1, in which said docosahexaenoic acid is present in said extract in a concentration which ranges between 5% and 100% (w/w).

        9. Use according to Claim 2, in which said docosahexaenoic acid is present in said extract in a concentration which ranges between 50% and 100% (w/w).

30        10. Use according to any of the preceding claims, in which the medicament is administered orally.

        11. Use according to any of the preceding claims, in which the medicament is administered parenterally.

        12. Use according to Claim 1, in which said mammal  
35 is a human.

13. Use according to Claim 12, in which said human  
is infected with the HIV virus.

**ABSTRACT**

Use of an extract of animal, plant or microorganism-produced origin comprising docosahexaenoic acid as active substance for the manufacture of a medicament for the treatment of lipodystrophy in a mammal.

Said treatment is effective and overcomes the disadvantages of current lipodystrophy treatments in HIV-infected patients.